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Filed: 12 June 1997

*Sub 1*  
*DO*  
*Revised*  
66. A composition comprising a deoxynucleotide triphosphate comprising a covalently attached metallocene.

67. A composition according to claim 66 wherein said metallocene is ferrocene.

### REMARKS

Claims 47-67 are pending. In the interest of clarity, old claims 33 and 36-46 have been canceled and new claims drafted.

Support for new claim 47 is found in old claim 33 and on page 65, line 5, to line 66, line 4.

Support for new claim 48 is found on pages 65, line 9 to page 66, line 19.

Support for new claim 49 is found in numerous places within the specification; *see* Structure 23 (page 41), Structure 27 (page 43), etc.

Support for new claims 50 and 51 is found in old claims 36 and 37 and on page 16, lines 1-25, page 18 line 25 to page 19, line 2, and page 25, line 19 to page 26, lines 13.

Support for new claim 52 is found in numerous places within the specification; *see* for example page 14, lines 6-13; page 27, line 14 to page 28, line 3.

Support for new claim 53 is found in numerous places within the specification; *see* for example page 71, lines 10-21.

Support for new claim 54 is found in numerous places within the specification; *see* for example on page 62, lines 4-13.

Support for new claim 55 is found in old claims 36 and 37 and on page 16, lines 1-25, page 18 line 25 to page 19, line 2, and page 25, line 19 to page 26, lines 13.

Support for new claims 56-58 is found in old claim 37 and on page 18 line 25 to page 19, line 2, and page 85, lines 11-24.

Support for new claims 56 and 59 is found in old claim 37 and on page 18 line 25 to page 19, line 2, page 45, lines 3-25 and page 47, lines 17-18.



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Support for new claims 60-61 is found on page 85, lines 11-14.

Support for new claims 62-67 is found in old claims 43 and 44 and on page 51, line 13 to page 58, line 11, and page 59, line 11-23.

In Figure 1, third reaction on the top line, "Bezene" has been changed to "Benzene." Applicants have enclosed a copy of Figure 1 with a redline through "Bezene" and a substitute Figure 1 with the corrected spelling for the solvent "Benzene."

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 36-39 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 36-39 have been canceled and the rejection is moot. However, the Examiner's attention is drawn to the claim amendments regarding B-D and C-G-C moieties. These amendments should obviate the rejection.

Anticipation Rejection Under 35 U.S. C. § 102(e)

Claims 58-76 are rejected under 35 U.S.C. § 102(e) as being unpatentable over Ribí et al.

As discussed during the interview, the Ribí et al. reference is somewhat confusing. The Examiner asked that applicants clearly point out in Ribí et al. the important concepts and distinctions.

Ribí et al. describes a system that utilizes at least four components: a substrate, a set of interdigitating electrodes, a polymerizable surfactant film that forms a crystalline structure, and at least one binding ligand ("a member of a specific binding pair").

Ribí's substrate is an insulative solid support (see column 3, line 19), and can be made of a variety of materials. Preferred embodiments utilize polystyrene (see column 4, line 36). It should be noted that polystyrene is not a conductive material, and is not used in Ribí et al. as such.

A "highly oriented polymerized surfactant film" (column 3, lines 19-20) is then added to the insulative substrate. This may be done covalently or non-covalently (see column 3,



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lines 37-41). This surfactant film is either electronically semi-conducting or variably conducting (see column 3, lines 21-22).

Binding members (i.e. for binding a target analyte) are then added to the surfactant film (sometimes also referred to in Ribí et al. as a lipid portion; see column 5, line 26). The binding members are generally added to the surfactant film by using a linker (see column 5, lines 25-56). These linkers are chosen depending on the "degree to which one wishes to perturb the electrical properties of the polymer" (see column 5, line 34-36). That is, as shown below, the mechanism of Ribí et al. relies on a change in the electromagnetic properties of the film as a result of the binding of a target analyte. Thus, Ribí et al. states that "[t]he more rigid and shorter the linker, assuming high affinity analyte binding, the greater the perturbation of the polymer upon binding of the specific binding member to its complementary member." (Column 5, lines 37-40).

In addition, this perturbation causes a change in the electrical properties of the surfactant due to the presence of dopants. These dopants (donors and acceptors) alter their orientation in response to the binding of the target analytes, thus causing the changes in the electrical properties of the film. See column 5, lines 59-64:

The orientation of the acceptor or donor molecule (dopant) with respect to the polymer lattice will affect the polymers' net electrical characteristics. The electrical properties of the film will be affected by analyte binding where the binding event causes a change in the orientation of the dopant molecule.

Generally, Ribí et al. appears to function in the following way. Upon binding of a target analyte, the electromagnetic properties of the film change (either its electronic or optical properties; see column 3, line 26) as a result of binding of a target analyte for detection. Therefore the film is the intervening medium between the two electrodes, and changes in the film's properties serve as the basis of the assay for the presence or absence of the target analyte.

Furthermore, in order to make this work (as shown in Figure 3, column 16, lines 27-31, and column 16, line 61 to column 17, line 42 ("Electrode Protection") of Ribí et al.), the electrodes must be electrically insulated from the aqueous medium using such things as parafilm, wax, nail polish, etc., so that direct electrical contact of two interdigitating electrodes does not occur. As the Examiner will appreciate, if there is direct electrical contact of the two electrodes



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through the aqueous media, the presence of charge carriers in the sample would provide two pathways for current flow: through the solution and through the film. Presumably this would be unacceptable.

As outlined above, Ribí et al. does not teach or suggest the compositions of the present invention. The present invention has conductive oligomers attached to both an electrode and the binding ligand, e.g. a nucleic acid. Ribí et al. does not outline covalent attachment of a conductive oligomer to the electrode; rather, in Ribí et al., the surfactant is attached to the insulative substrate. As will be appreciated in the art, Ribí's disclosed methods of forming electrodes on the surfaces are non-covalent methods such as "painting" the electrodes onto the substrate (see the Examples, column 27, lines 5-10) and photoresist/etching methods (see column 10, lines 17-31).

In addition, the present invention does not rely on a change in conductivity of the conductive oligomers as a result of binding of a target analyte for detection. That is, the conductive oligomers of the invention do not change their conductivity as a result of analyte binding. Rather, the present invention relies on electron transfer between the ETMs of the invention and the electrode.

The Examiner's main point appears to be that Ribí et al. teaches the compositions of the invention because Ribí suggests the use of polystyrene, and polystyrene is a "conductive oligomer" as defined within the specification. The applicants respectfully disagree, and point out that in fact, those of skill in the art consider polystyrene to be an electrical insulator, not a conductor.

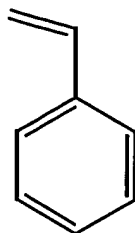
As a preliminary matter, Ribí et al. teaches the use of polystyrene as an insulating substrate, not as a conductive oligomer. See Ribí et al., column 3, lines 45 to column 4, line 33.

Furthermore, the applicants point out that polystyrene does not fit into the formula depicted in Structure 2. The structure of styrene, prior to polymerization, is shown below:



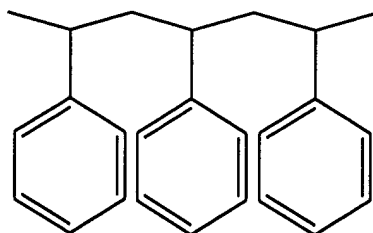
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Styrene



After polymerization, polystyrene has the structure:

Polystyrene



Thus, the applicants note that this structure does not fit into the definition of Structure 2. There is no aromatic group that is part of the backbone of the chain.

In further support of the proposition that polystyrene is not a conductive oligomer, and is in fact an insulator, the applicants submit the declaration of Dr. Gary Blackburn, the Vice President of Scientific Affairs of Clinical Micro Sensor, Inc., the assignee of the present application. Dr. Blackburn states that polystyrene is not a conductive oligomer as defined in the specification, and is in fact considered by those in the art to be an electrical insulator.

In support of his position, Dr. Blackburn submits three Exhibits that show that polystyrene is considered by those in the art to be an insulator and is used as one. For example, Morrison & Boyd (Organic Chemistry, 3rd Edition, Allyn and Bacon, Inc., 1973, pages 1030 to 1033, a copy of which is enclosed as Exhibit A) describes polystyrene as an electric insulator:

Consider, for example, styrene. Polymerized alone, it gives a good electric insulator that is molded into parts for radios, television sets, and automobiles.

See page 1033, third paragraph in section 32.4.



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Similarly, as shown in Oxtoby & Nachrieb (Principles of Modern Chemistry, 3rd Edition, Saunders College Publishing, 1996, page 828, a copy of which is enclosed as Exhibit B), shows that polystyrene is used as insulation (see Table 23-5).

Furthermore, as shown in Mazda (Electronics Engineer's Reference Book, 5th Edition, Butterworth & Co., 1983, pages 13/9 and 13/10, a copy of which is enclosed as Exhibit C), shows that polystyrene is used as in plastic-dielectric capacitors. As stated,

In plastic-dielectric capacitors the dielectric consists of thin films of synthetic polymer material. The chief characteristic of plastic-film capacitors is their very high insulation resistance at room temperatures. The main synthetic polymer films used as capacitor dielectrics are: . . . polystyrene.

See first paragraph of section 13.2.8 on page 13/9 and the first paragraph on page 13/10. Table 13.3 on page 13/10 shows some of the properties of these film materials.

As Dr. Blackburn concludes, "polystyrene is well-known to be an electrical insulator, and would not be considered by those of skill in the art to be a "conductive oligomer" as defined in the application".

Accordingly, the applicants submit that Ribí et al. does not anticipate the present invention, and thus the rejection under §102(e) should be withdrawn.

#### Double Patenting Rejection Under 35 U.S.C. § 101

Claims 33, 36, 37 and 39-44 are provisionally rejected under § 101 as claiming the same invention as claims 29 and 32-39 of co-pending application U.S.S.N. 08/743,798.

It is the applicants intention to cancel the non-elected claims in U.S.S.N. 08/743,798; accordingly, applicants respectfully request the rejection be held in abeyance until otherwise allowable subject matter is found.

The applicants submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited. If after review of the amendment, the Examiner



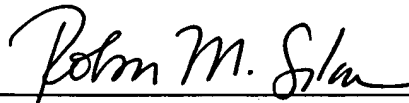
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feels that there are further remaining issues, the applicants respectfully request the Examiner call the undersigned, Robin M. Silva, at (415) 781-1989.

Dated: 1 November 1999

Respectfully submitted,

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# Synthesis Scheme of Wire-Aminouridine-Succinate

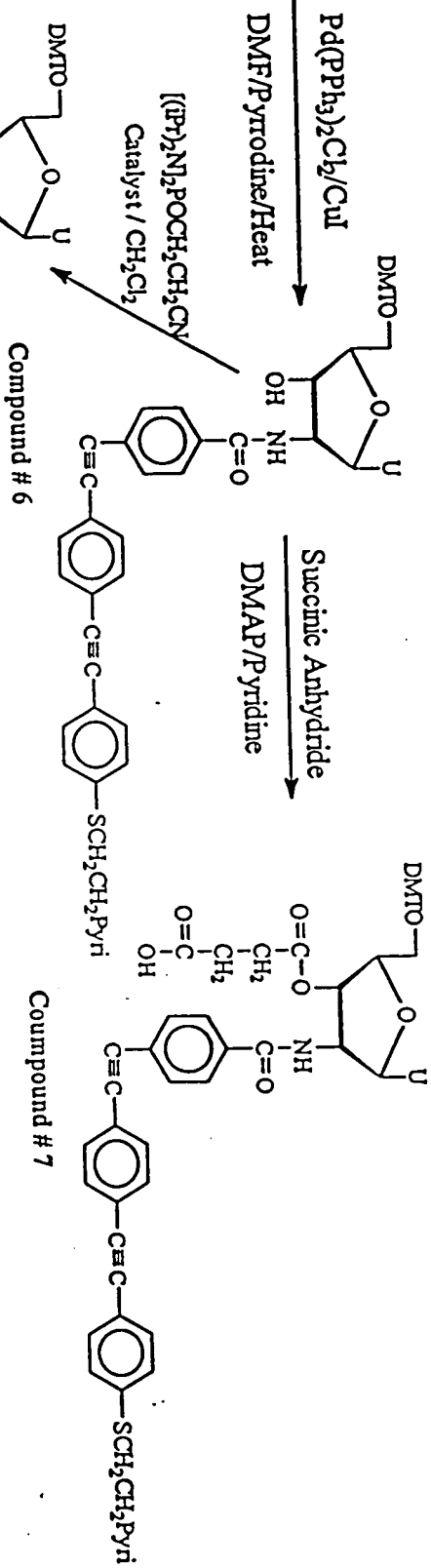
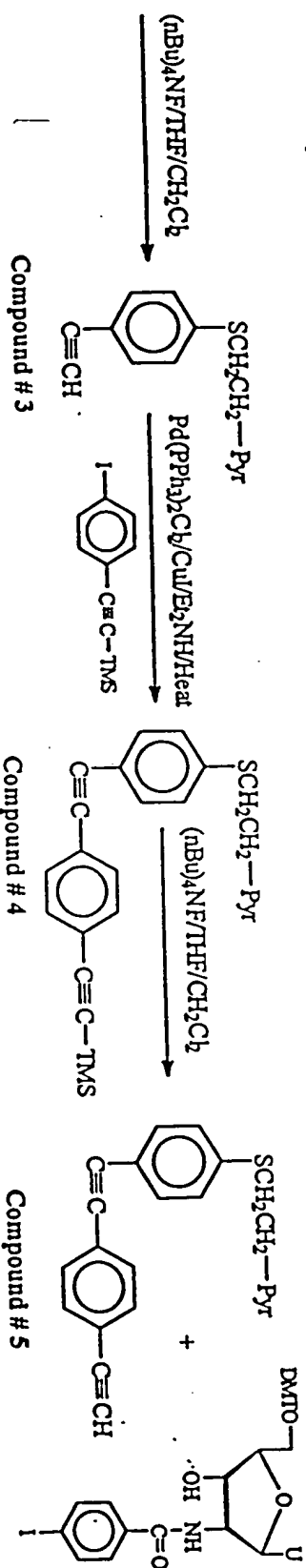
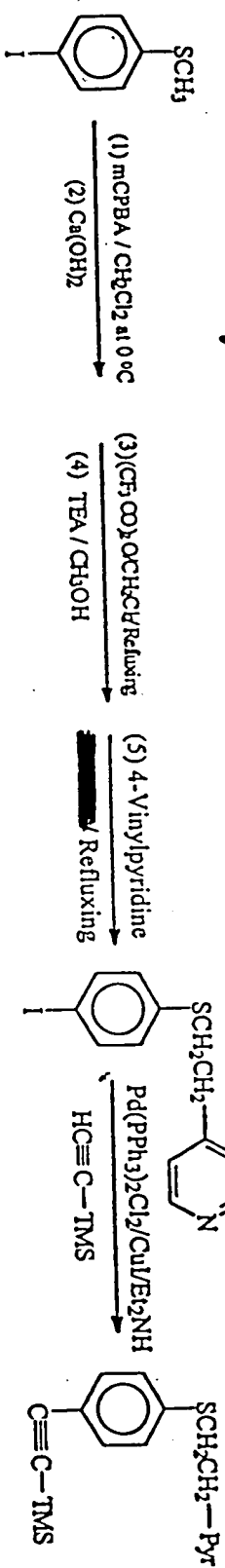


FIGURE 1